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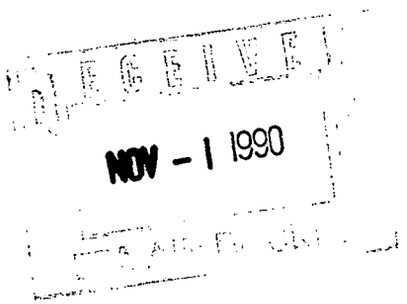

October 31, 1990

Public Docket A-90-16
Air Docket (LE-131)
EPA 401 M Street, SW
Room M-1500
Washington, DC 20460

Dear Sir/Madam:

On behalf of Chemetals, Inc. (711 Pittman Road, Baltimore, MD 21226), enclosed are additional comments on the waiver request of Ethyl Corporation for the use of HiTEC 3000 in unleaded gasoline in the United States.

Sincerely yours,

ACKolbye

Albert C. Kolbye, Jr., M.D., M.P.H., J.D.
Director, Kolbye Associates

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ADDENDUM FROM KOLBYE ASSOCIATES CONCERNING MANGANESE IN AIR

During a recent meeting (19 October 1990) between Chemetals, Inc. and EPA officials, the latter raised several questions of concern to them. This addendum is divided into three parts: manganese levels in air, manganese inhalation studies in non-human primates, and manganese studies on patients with Alzheimer's Disease or other forms of dementia.

MANGANESE LEVELS IN AIR

First was a question of how representative the mean air concentrations of manganese actually were in view of their allegations that some air monitoring stations had picked up to 20 times higher levels. Without knowing their data, it would be expected that from time to time and place to place, higher air levels of manganese can be found.

Explanations are likely to involve proximity to point sources of manganese emissions such as ferromanganese smelting and alloy production sites, welding activities, or airborne ground-dust on windy days.

Welding activities usually involve fumes and such point sources should be controlled for reasons of occupational and environmental health. They are not part of the HiTec3000 consideration, nor are smelters and airborne ground-dust.

Smelters fall into the same category as welding operations and airborne emissions should be properly controlled.

Airborne ground-dust may contain appreciable quantities of manganese but frequently involves relatively large particle sizes greater than 10 microns and hence will not be respirable. If some particles are inhaled very little will remain in the lung as most will be exhaled and much of the remaining residue will be expelled out of the respiratory system by mucociliary activity in the bronchial tubes or nasopharynx and either expectorated or swallowed. In the latter case, very little -under 4%- will be absorbed from the gastrointestinal tract into the mammalian body and when it is, homeostatic mechanisms of control and excretion will take over. Such airborne ground-dust is not relevant to the HiTec3000 considerations; ground-dust has been airborne since time immemorial. There is no record of manganism from such exposures unless very intensive point sources such as mining or smelting are involved.

It is clear that only very negligible amounts of additional airborne manganese will arise from the usage of HiTec3000 in automotive fuels. The additional fraction is estimated to be within a few percent (maximum about 10%) of airborne manganese presently encountered from sources other than HiTec 3000.

If HiTec3000 is used as a fuel additive, automobile exhaust emissions at the "worst case assumptions" level were estimated to approximate 500 nanograms/M3 of actual tailpipe exhaust by the Health Effects Institute.[1] 1500 nanograms/M3 in tailpipe exhaust have been estimated by Ethyl Corporation in the waiver application[2]. These emissions then would immediately be diluted into the local atmosphere. Over a very short time, such dilution would normally be several hundreds or thousands-fold, depending upon air circulation, thus reducing the levels of manganese in air to those approximating ambient ones. Even in the Pennsylvania Turnpike studies during the mid-1970s, the tunnel air contained only an average of 110 nanograms/M3 of manganese. How much was respirable is not given. National Air Surveillance Network data shows that the highest urban air concentration of manganese between 1972 and 1982 was 34 nanograms/M3 and the highest 95th percentile was 120 nanograms/M3.[3] In the same reference, higher levels from 300 to over 1000 nanograms/M3 have been reported near foundries and ferromanganese plants, respectively.

Another consideration has been introduced by EPA in its HAD of 1984: that of particle size in relation to concentration of manganese. "More recent data tend to indicate that less of the ambient manganese is found in fine particles."[4] The text goes on to say that the average percentage of manganese in fine (under 2.5 microns) particles was 28% or in effect, 16% of measured manganese. By implication, except for unusual situations, most of the airborne manganese is in the "coarse" particles ranging from 2.5 to 15 microns. The coarser particles are much less likely to be absorbed through the alveolar membrane into systemic circulation and are more likely to be excreted from the pulmonary tract.[5] Of additional interest is EPA's estimate that: "Alveolar deposition of manganese at current ambient levels is estimated as 0.072 micrograms/day (average) and 6.6 micrograms/day (high). Estimates of total thoracic deposits are slightly higher. Alveolar and total thoracic deposition under high exposure conditions in the 1960s were

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[1] Health Effects Institute report,1988

[2] Assumptions underlying calculations:
5 micrograms Mn/mile emission
25 mpg
2.0 liter engine
2000 rpm
15 inches Hg manifold vacuum

[3] Health Effects Institute,1988 @ p.8

[4] EPA-HAD,1984 @ p.3-74

[5] See discussion in EPA-HAD, 1984 @ pp. 3-83 and 3-84.

estimated to be as high as 100 and 152 micrograms/day, respectively."[6] These estimates refer to ambient air without MMT.

While tailpipe emissions of manganese from vehicles using MMT in HiTec3000 are initially in the lower size range, such residues in air will be diluted very substantially and, by estimate are unlikely to contribute more than a few nanograms to ambient air concentrations of manganese. If automotive emissions of manganese are adsorbed onto the surfaces of larger particles in automotive emissions or in the ambient air, they are far less likely to be respirable and accordingly are far less likely to be absorbed through the alveolar membrane into the human body. When they settle to the ground surface, they will become identical to manganese in ground-dust.

> Conclusion: Of ambient manganese, only a minor fraction is respirable. Of 34 nanograms/M3 in ambient air, probably only 10 nanograms are in the respirable range. Additional respirable manganese added to air from usage of MMT in HiTec 3000 is unlikely to exceed a few nanograms. There should be no problem whatsoever with this negligible addition.

MANGANESE INHALATION STUDIES IN NON-HUMAN PRIMATES

Concern was also raised by EPA about the adequacy of dose-response data from inhalation studies of manganese toxicity. Rodents such as mice, guinea pigs, hamsters and rats all are obligate nose breathers. Consequently their anatomical characteristics of narrow and convoluted nasal turbinates and narrow pulmonary airways are extreme confounding and interfering factors for accurate assessments of inhalation toxicity. Although rodents have been used in large numbers since they are relatively cheap and logistically easy to manage, anatomical and physiological differences can render them irrelevant for particular purposes.

When testing for manganese toxicity, almost all species have many similar behavioral and pathological changes when effective doses are given by whatever route of administration. These include neurotoxicity findings. However, non-human primates have larger airways and more closely resemble humans with regard to naso-pharyngeal and pulmonary anatomy and physiology. In many other ways they also resemble humans much more than do rodents. They are relatively expensive and much more laboratory support is required to perform experiments. Also, some primates such as chimpanzees are in very short supply and subject to higher priorities for testing purposes that benefit society. Hence, fewer primates are tested than rodents and the number of primates per experiment is usually far less than that of rodents.

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[6] EPA-HAD, 1984 @ p. 3-85.

Toxicological experiments conducted in lesser numbers of non-human primates usually have much greater relevance to human health considerations than do rodent studies involving larger numbers of rodents on test. This is especially true with regard to inhalation toxicology because of the anatomical and physiological considerations mentioned earlier.

Under EPA contract, Coulston and Griffin reported in 1976 on "Inhalation Toxicology of Airborne Particulate Manganese in Rhesus Monkeys". Rats were also studied. Four male and four female rhesus monkeys were exposed and three more monkeys of each sex served as non-exposed controls. Dietary manganese averaged 47 mg/ gram of monkey chow. Water manganese ranged from 0.17 to 0.33 micrograms/ml. For periods lasting up to 66 weeks, these male and female rhesus monkeys were exposed by inhalation to manganese in air at a concentration of 100 micrograms/M3 (100,000 nanograms/M3) for 23 hours/day. (Rats received similar exposures for up to 8 weeks.) Additionally, two rhesus monkeys were exposed by inhalation to 5 mg/M3 (5000 micrograms/M3 or 5,000,000 nanograms/M3) of manganese in air for 23 hours/day for 23 weeks and then observed for an additional 10 months. Excretion of manganese reflected dietary intake, not air intakes. Minor manganese residue accumulation occurred in visceral tissues, and an average of twice-normal residues were detected in the central nervous system. No morphological changes were detected after pathology examination. (Rats accumulated manganese in lung and brain but quickly reverted to normal after removal from exposure for one week.) No adverse effects such as neurological disorders in the animals were noted. The source of airborne manganese exposure was MMT combusted in air by natural gas.[7]

> Conclusion: At 1000 and 50,000 times expected human exposure under worst environmental conditions (assumed to approximate 100 nanograms/M3 of manganese in air including from MMT) no effects other that slight tissue accumulation and increased excretion were noted in rhesus monkeys exposed by inhalation for substantially long periods of time.
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> If combusted MMT were involved as a source for human exposure to manganese, comparable test exposures in this experiment for respirable manganese would still have been the same because the assumption for this author's analysis of potential human exposure was a high estimate of 100 nanograms/M3 of total manganese. Actually the respirable portion of the total particulate average

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[7] "Inhalation Toxicology of Airborne Particulate Manganese in Rhesus Monkeys, EPA contract 68-02-0710, reported in November, 1976 by Frederick Coulston, Ph.D. and Travis Griffin, Ph.D. of Albany Medical College and Holloman Air Force Base, New Mexico.

ambient range of 34 nanograms/M3 average manganese residues in air is about 10 nanograms/M3 without MMT usage. With MMT usage, a reasonable estimate is an additional few nanograms/M3 of respirable manganese, which is still very far below the conservative estimate of 100 nanograms used for this analysis. Thus, the actual experimental dosage margins approximated 10,000 and 500,000 times anticipated human exposure to respirable manganese in air including MMT usage. While some tissue accumulation of manganese in rhesus monkeys did occur, there were no discernible pathological effects seen, including neurobehavioral. Granted that these were not lifetime exposures, but the exposures were of sufficient duration, frequency and intensity that if pathological findings were to occur, they should have been noticed under these experimental conditions. **When normal safety factors of 100[8] are used for a non-carcinogenic substances, we can see that we have a safety margin approximating 100 to 5000 times the normal safety margin of 100.**

Squirrel monkeys (32) were divided into four groups, each containing 4 males and 4 females.[9] One group served as controls and the other three were exposed 24 hours/day to inhaled manganese from MMT combusted in propane resulting in manganese air concentrations of 10, 100, and 1000 micrograms/M3. Half the monkeys were exposed for 9 months and then sacrificed; the remaining monkeys were observed post-exposure for an additional 6 months prior to sacrifice and examination. No adverse effects related to manganese exposure were reported. Extensive clinical, laboratory and pathology examinations were conducted including tissue residue studies. No problems were encountered.

Conclusion: In a different species of non-human primate, again no adverse effects were noted at the doses studied. **These inhalation exposures to manganese that caused no adverse effects in squirrel monkeys were at 100, 1000 and 10,000 times greater than anticipated human exposures at**

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[8] The U.S. Food & Drug Administration uses a safety factor of 100 times the highest no-adverse effect level for lifetime studies in rodents administered the test compound. Even though the non-human primate studies were less-than-lifetime, their relevance to human health considerations are far higher than dose-response data generated from studies in rodents. Even if we subtracted a factor of 10 to allow for subtle adverse effects, we still see very substantial safety margins.

[9] Huntingdon Research Center 1975 report to Ethyl Corporation, Project Number 731-339.

worst case, if 100 nanogram/M3 is used as an assumption. This assumption includes usage of MMT.

The two studies of the effects of combusted MMT in monkeys are notable for many reasons. The animals were directly exposed to manganese from combusted MMT, so that particle size conditions referable to human exposure were duplicated. Their airways, lungs and central nervous systems closely mimic human counterparts.

No adverse pathology or neurobehavioral changes were noted although some tissue accumulation was noted in extremely high dose exposure conditions. These are not relevant to the levels of anticipated human exposure in non-occupational settings.

MANGANESE STUDIES ON PATIENTS WITH ALZHEIMER'S DISEASE OR OTHER FORMS OF DEMENTIA

It is well known that aluminum and silicon are more highly concentrated in the neurofibrillary tangles that comprise the microscopic lesions noted in the brain tissues of patients with Alzheimer's Disease. Whether these are causes or associated effects is not known because the etiologic factors that cause this disease are not completely understood; a viral etiology has not been excluded as the primary cause. But manganese has been studied in relation to these diseases and to other forms of dementia. No significant differences in manganese concentration levels in brain tissues of Alzheimer's patients were noted in three different reports by Markesbery et al (1984)[10], Shore et al (1984)[11], and Hershey et al (1983)[12]. While chronic manganism is known to be associated with brain disease similar to Parkinson's Syndrome, there is no credible evidence that manganese is contributing to dementia in the elderly.

SUMMARY: The concentrations of manganese in air are not significantly increased from usage of MMT in HiTec3000. Non-human primates tolerate long-term exposures to combusted MMT very well. No linkage has been established between manganese and the dementias of the elderly such as Alzheimer's Disease.

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[10] Markesbery et al, Neurotoxicology 5 (1): pp.49-57, 1984.

[11] Shore et al, Journal of American Geriatric Society, 32 (12): pp. 892-895, 1984.

[12] Hershey et al, Neurology 33 (10): pp. 1350-1353, 1983.